



05-23-01 JC19 Rec'd PCT/PTO 22 MAY 2001 PCT

DRM PTO-1390 DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE (REV 1-98)		ATTORNEY'S DOCKET NO 4040.000300
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		U.S. APPLICATION NO. (If known, see 37 CFR 1.57) 09/856400 UNKNOWN
INTERNATIONAL APPLICATION NO. PCT/GB99/03952	INTERNATIONAL FILING DATE November 26, 1999	PRIORITY DATE CLAIMED November 26, 1998
TITLE OF INVENTION Anti-Asthmatic Combinations Comprising Surface Active Phospholipids		
APPLICANT(S) FOR DO/EO/US Brian Andrew Hills, Derek Alan Woodcock and John Nicholas Staniforth		
Applicants herewith submit to the United States Designated/Elected Office (DO/EO/US) the following items and other information:		
<ol style="list-style-type: none"><input checked="" type="checkbox"/> This is a FIRST submission of items concerning a filing under 35 U.S.C. 371.<input type="checkbox"/> This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371.<input checked="" type="checkbox"/> This is an express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).<input checked="" type="checkbox"/> A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.<input checked="" type="checkbox"/> A copy of the International Application as filed (35 U.S.C. 371(c)(2)).<ol style="list-style-type: none"><input checked="" type="checkbox"/> is transmitted herewith (required only if not transmitted by the International Bureau); PCT cover page; 30 pages of text, Figures 1-3 on 2 sheets, and 6 pages of Search Report.<input type="checkbox"/> has been transmitted by the International Bureau.<input type="checkbox"/> is not required, as the application was filed in the United States Receiving Office (RO/US).<input type="checkbox"/> A translation of the International Application into English (35 U.S.C. 371(c)(2)).<input type="checkbox"/> Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)).<ol style="list-style-type: none"><input type="checkbox"/> are transmitted herewith (required only if not transmitted by the International Bureau).<input type="checkbox"/> have been transmitted by the International Bureau.<input type="checkbox"/> have not been made; however, the time limit for making such amendments has NOT expired.<input type="checkbox"/> have not been made and will not be made.<input type="checkbox"/> A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).<input type="checkbox"/> An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).<input type="checkbox"/> A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).		
Items 11 to 16 below concern document(s) or information included:		
<ol style="list-style-type: none"><input type="checkbox"/> An Information Disclosure Statement under 37 CFR 1.97 and 1.98.<input type="checkbox"/> An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included and the fee is incorporated within the attached check.<input checked="" type="checkbox"/> A FIRST preliminary amendment (with Exhibits A, B and C); please calculate the filing fee based upon the claims in this amendment. <input type="checkbox"/> A SECOND or SUBSEQUENT preliminary amendment.<input type="checkbox"/> A substitute specification.<input type="checkbox"/> Power of attorney and/or address letter.<input checked="" type="checkbox"/> Other items or information: 1. PCT Request; 2. International Search Report; 3. PCT Demand; 4. International Preliminary Examination Report (IPER) with annex; and 5. Postcard		

09/856400

CERTIFICATE OF EXPRESS MAILING	
NUMBER	EL 522 496 775 US
DATE OF DEPOSIT	May 22, 2001
I hereby certify that this paper or fee is being deposited with the United States Postal Service "EXPRESS MAIL POST OFFICE TO ADDRESSEE" service under 37 CFR 1.10 on the date indicated above and is addressed to Assistant Commissioner for Patents, Washington, DC 20231	
<i>Kathy Danas</i> Kathy Danas	

U.S. APPLICATION NO. (If known, see 37 CFR 1.5) UNKNOWN	INTERNATIONAL APPLICATION NO. PCT/GB99/03952	ATTORNEY'S DOCKET NUMBER 4040.000300
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17. ☒ The following fees are submitted:

Basic National Fee (37 CFR 1.492(a)(1)-(5)):
 Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO \$1,000.00

International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO \$860.00

International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO \$760.00

international preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) \$690.00

International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) \$ 100.00

ENTER APPROPRIATE BASIC FEE AMOUNT				=	\$ 860.00	
Surcharge of \$130.00 for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input checked="" type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(e)).				\$		
Claims	Number Filed	Number Extra	Rate			
Total Claims	38 - 20 =	18	x \$ 18.00	\$	324.00	
Independent Claims	7 - 3 =	4	x \$ 80.00	\$	320.00	
Multiple dependent claim(s) (if applicable)			+ \$260.00	\$	260.00	
TOTAL OF ABOVE CALCULATIONS				=	\$ 1,764.00	
Reduction by 1/2 for filing by small entity, if applicable. Verified Small Entity Statement (no longer necessary)				\$		
SUBTOTAL				=	\$ 1,764.00	
Processing fee of \$130.00 for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(f)).				\$		
TOTAL NATIONAL FEE				=	\$ 1,764.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40.00 per property)				+	\$ -0-	
TOTAL FEES ENCLOSED				=	\$ 1,764.00	
					Amount to be refunded	\$.00
					Charged	\$.00


a. ☒ A check in the amount of \$1,764.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. _____ in the amount of \$ _____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 50-0786/4040.000300. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO.
 Shelley P.M. Fussey
 WILLIAMS, MORGAN & AMERSON
 7676 Hillmont, Suite 250
 Houston, TX 77040
 (713) 934-7000
 Date: May 22, 2001



SIGNATURE
 Shelley P.M. Fussey

NAME:
 39,458

REGISTRATION NUMBER:

09/856400

09/856400

JC18 Rec'd PCT/PTO 2 2 MAY 2001

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Hills *et al.*

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Group Art Unit: Unknown

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Serial No.: Unknown

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PCT/GB99/03952

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Examiner: Unknown

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Filed: May 22, 2001

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Intl. Filing date: November 26, 1999

§

Atty. Dkt.: 4040.000300

Priority date: November 26, 1998

§

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For: Anti-Asthmatic Combinations

§

Comprising Surface Active

§

Phospholipids

§

EXPRESS MAILING LABEL

37 C.F.R. § 1.10

I hereby certify that this paper is being deposited with the U.S. Postal Service "EXPRESS MAIL POST OFFICE TO ADDRESSEE" (Number EL 522 496 775 US) service on the date indicated and is addressed to Assistant Commissioner for Patents, Washington, D.C. 20231, on the date below:

May 22, 2001

Date



Kathy Danas

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents

BOX PCT

Washington, D.C. 20231

Sir:

The present document is a Preliminary Amendment filed in conjunction with the nationalization of International Patent Application PCT/GB99/03952. After entry into the U.S. national stage, and assurance of a U.S. filing date, entry of the following amendments is respectfully requested. Any omitted fees are authorized to be deducted from Williams, Morgan & Amerson, P.C. Deposit Account No. 50-0786/4040.000300.

09856400-09401

AMENDMENT

In the Specification:

Prior to page 1, where the text of the application begins, please delete the double-sided cover page from the PCT stage if necessary.

At page 1, after the title, in the current single-paragraph that constitutes the entire Section of the Application pertaining to "Cross-Reference to Related Applications", please delete the existing section and replace such deleted section with the following, two-paragraph replacement section:

The present application is a nationalization of International Patent Application PCT/GB99/03952, filed November 26, 1999, which claims priority to British Patent Application 9912639.3, filed May 28, 1999 and to International Patent Application PCT/GB98/03543, filed November 26, 1998.

Field of the Invention

This invention relates to pharmaceutical products for use in the treatment of asthma and to delivery devices including the products.

After page 30, please start another page (31), and insert the following text of the Abstract, as taken from the cover page of the PCT application:

ABSTRACT

Disclosed is a combination product for use in treating asthma and other respiratory conditions comprising a medicament comprising a surface active phospholipid composition in the form of a fine powder and an antiasthma drug. The product is arranged to be administered to the lungs by inhalation, for example, by the disclosed devices.

At the appropriate pages, prior to the text on each page, please delete the header that reads "WO 00/30654 PCT/GB99/03952" if necessary.

In the Claims:

After entry into the U.S. national stage, and assurance of a U.S. filing date, please revise the claims from the enclosed published PCT application as follows.

Please amend published PCT claims 1, 6, 8, 10, 11, 14-30 and 32-34, so that the rewritten claims read as follows:

1. (Amended) A therapeutic combination product for use in the prevention and/or treatment of asthma comprising (a) a medicament comprising a surface active phospholipid (SAPL) composition in finely divided form, the SAPL composition including a component which enhances spreading of the medicament over a surface at about normal mammalian body temperature and (b) an antiasthma drug, wherein ingredients (a) and (b) are provided in a form for administration together or separately.
6. (Amended) A combination product as claimed in claim 2, in which the medicament (a) comprises a phosphatidyl glycerol.
8. (Amended) A combination product as claimed in claim 2, in which the medicament (a) comprises one or more compounds selected from the group consisting of diacyl phosphatidyl cholines.
10. (Amended) A combination product as claimed in claim 2, in which the medicament (a) is in micronised form.

11. (Amended) A combination product as claimed in claim 2, in which said medicament (a) has a median particle size not exceeding 10 μ m.

14. (Amended) A combination product as claimed in claim 2, in which the antiasthma drug comprises one or more respiratory drugs selected from the group consisting of β_2 -agonists, steroids, cromones, antimuscarinic drugs and leukotriene receptor antagonists.

15. (Amended) A combination product as claimed in claim 14, which comprises one or more of said antiasthma drugs in an amount of up to 10 parts by weight per hundred parts by weight of said first and second components of medicament (a) in combination.

16. (Amended) A combination product as claimed in claim 15, which comprises one or more of said respiratory drugs in an amount of up to one part by weight per hundred parts by weight of said first and second components of medicament (a) in combination.

17. (Amended) A combination product as claimed in claim 14, in which ingredient (b) comprises a β_2 -agonist.

18. (Amended) A combination product as claimed in claim 14, in which ingredient (b) comprises a steroid.

19. (Amended) A combination product as claimed in claim 14, in which ingredient (b) comprises a cromone.

20. (Amended) A combination product as claimed in claim 14, in which ingredient (b) comprises a leukotriene receptor antagonist.

21. (Amended) A combination product as claimed in claim 14, in which ingredient (b) comprises an antimuscarinic drug.

22. (Amended) A combination product as claimed in claim 2, in which at least ingredient (a) is arranged to be delivered to a patient in the form of at least one individual inhalable dose, the individual dose or each individual dose comprising said ingredient (a) in an amount of at least 10mg.

23. (Amended) A combination product as claimed in claim 22, in which the individual dose or each individual dose comprises said first and second components in a combined amount of at least 25mg.

24. (Amended) A combination product as claimed in claim 23, in which the individual dose or each individual dose comprises said ingredient (a) in a combined amount of at least 40mg.

25. (Amended) A combination product as claimed in claim 22, in which at least ingredient (a) is arranged for sequential delivery of a multiplicity of inhalable doses.

26. (Amended) A combination product as claimed in claim 1 or claim 2, in which the antiasthma drug is arranged for delivery in admixture with ingredient (a).

27. (Amended) A combination product as claimed in claim 1 or claim 2, in which the antiasthma drug is arranged for delivery separately from, and simultaneously or sequentially with, ingredient (a).

28. (Amended) A pack for use as part of a combination product according to claim 1 or claim 2, said pack including a delivery device for delivery of ingredient (a) to a patient and further comprising instructions to use said delivery device in a method of treatment including the separate simultaneous or sequential administration of an antiasthma drug.

29. (Amended) A method of prevention and/or treatment of asthma, comprising administering to a patient at least one dose of a combination product as defined in claim 1 or claim 2.

30. (Amended) A delivery device for administering to a patient by inhalation a medicament for the prevention and/or treatment of asthma, the delivery device containing a medicament comprising a surface active phospholipid (SAPL) composition in finely divided form, the SAPL composition including a component which enhances the spreading of the medicament, the delivery device being arranged for delivery of at least one individual dose of the SAPL composition in an amount of at least 10mg.

32. (Amended) A delivery device as claimed in claim 30, in which the medicament is as defined in claim 2.

33. (Amended) A delivery device as claimed in claim 30 or 31, which further includes means for dispensing an inhalable dose of an antiasthma drug.

34. (Amended) A medicament for use in the control of asthma, comprising (a) a surface active phospholipid (SAPL) composition in finely divided form conjointly with (b) an antiasthma drug.

REMARKS

I. Nationalization

This application represents the U.S. national stage of International Patent Application PCT/GB99/03952, filed November 26, 1999, which claims priority to British Patent Application 9912639.3, filed 28 May, 1999 and to International Patent Application PCT/GB98/03543, filed November 26, 1998.

As the text of the International Application was transmitted by the International Bureau, an additional copy is not required to satisfy 35 U.S.C. § 371(c)(2). Nonetheless, for the Examiner's convenience, a copy of international application PCT/GB99/03952 is enclosed in the form of the published PCT Application WO 00/30654.

Although claim amendments were made during PCT examination, for the convenience of the U.S. examiner, the unamended claims of the published PCT Application form the initial basis of the present claims and any amendments thereto are clearly shown in the attached exhibits.

III. Status of the Claims

In the published PCT Application, claims 1-35 were pending. At the conclusion of the PCT examination phase, as indicated in the enclosed IPER, claims 1, 16 and 30 had been amended. All claims have unity of invention.

Presently, starting from the claims of the published PCT Application, claims 1, 6, 8, 10, 11, 14-30 and 32-34 have been amended to correct minor typographical oversights, to remove multiple dependencies and otherwise place the claims in better form for U.S. practice. No claims have been canceled or added. Claims 1-35 are therefore in the case.

IV. Support for the Claims

Aside from the procedural changes and typographical corrections, current claims 1-35 represent the claims at the conclusion of PCT examination. The changes generally fall into the following categories: to match the clarifications made during the PCT stage (claims 1 and 16), to correct minor typographical oversights (claims 10, 15, 16, 22, 23, 24 and 30), to accord with U.S. statutory subject matter (claim 34) and to remove multiple dependencies for U.S. practice (the remaining amended claims).

Support for the claim revisions largely exists in the amended claims themselves, as supplemented by original claims and specification as filed.

In particular, "composition" has been added to claim 1, and "delivery vehicle" has been changed to "combination product" in claim 16, each of which clarifications reflect those in the PCT phase.

Claims 10, 15 and 16 have been revised to correct minor grammatical errors in connection with "medicament (a) is in micronised form" and "one or more of said antiasthma drugs", respectively.

In claims 22, 23 and 24, the original language "the or each" has been improved by inserting another instance of "individual dose", so that the text now reads "the individual dose or each individual dose".

Claim 30 has been revised to add "composition" after the second instance of SAPL, as in claim 1, and to add "of the SAPL composition" in the last clause, which corresponds to a clarification made in the PCT phase.

Finally, claim 34 has been revised to change the non-statutory second medical use claim format into a composition claim drawn to the recited medicament, in accordance with 35 U.S.C. § 101.

The remaining changes to the revised claims simply remove the multiple dependencies, and such changes are clearly supported by each claim itself.

It will therefore be understood that no new matter is encompassed by any of the amended claims.

V. Compliance with 37 C.F.R. § 1.121

Copies of the pending claims are attached hereto as **Exhibit A** and **Exhibit B**. In accordance with 37 C.F.R. § 1.121, the claims have been labeled as "(Amended)", where appropriate. **Exhibit A** provides a clean copy of the pending claims, whereas **Exhibit B** shows the changes with brackets and underlining in reference to the claims published in the PCT application. As the claims with the IPER were not annotated, this is believed to be the best mechanism for complying with 37 C.F.R. § 1.121.

The proper claim for priority has been timely introduced into the specification by amendment of the opening paragraph at page 1. An Abstract of less than 200 words is also introduced into the specification by amendment as a separate page.

The amendments to the opening paragraph at page 1 of the specification and the abstract have been made as "Replacement Sections" in accordance with 37 C.F.R. §§ 1.121(b)(2), 1.77(b)(2) and 1.77(b)(10). This is proper under 37 C.F.R. §§ 1.121(b)(2)(i)(ii)(iii) as the amendments include specific instructions, replacement section in clean form and another version of the replacement section separate from the amendment marked up to show all changes (Exhibit C).

VI. Fees and Formalities

The national filing fee and claim fees are included herewith. The fees have been calculated **after** the changes to remove most multiply dependent claims. Any omitted fees should be deducted from Williams, Morgan & Amerson, P.C. Deposit Account No. 50-0786/4040.000300.

The claim fees have been calculated according to the following designations: independent, claims 1, 28, 29, 30, 31, 34 and 35; multiply dependent, claims 26, 27 and 33; and dependent, claims 2-25 and 32. Although claims 28 and 29 include a reference to claims 1 or 2 within the body of the claim, these are not multiply dependent claims as the preamble of each claim ("a pack" and "a method") shows that the claims do not depend from the "combination products" of claims 1 and 2. Nonetheless, as established in the PCT phase, all pending claims define a unified invention.

Should the Examiner have any questions or comments, a telephone call to the undersigned Applicants' representative is earnestly solicited.

Respectfully submitted,



Shelley P.M. Fussey
Reg. No. 39,458
Agent for Applicant

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Date: May 22, 2001

**EXHIBIT A
PENDING CLAIMS**

1. (Amended) A therapeutic combination product for use in the prevention and/or treatment of asthma comprising (a) a medicament comprising a surface active phospholipid (SAPL) composition in finely divided form, the SAPL composition including a component which enhances spreading of the medicament over a surface at about normal mammalian body temperature and (b) an antiasthma drug, wherein ingredients (a) and (b) are provided in a form for administration together or separately.
2. A combination product as claimed in claim 1, in which the ingredient (a) consists of a first component comprising one or more phosphatidyl cholines and a second component comprising one or more compounds selected from the group consisting of phosphatidyl glycerols, phosphatidyl ethanolamines, phosphatidyl serines, phosphatidyl inositols and chlorestyl palmitate.
3. A combination product as claimed in claim 2, in which medicament (a) comprises said first component and said second component in a weight ratio of from 1:9 to 9:1.
4. A combination product as claimed in claim 3, in which the proportion by weight of said first component exceeds that of said second component.
5. A combination product as claimed in claim 4, in which said first component and said second component are present in a weight ratio of from 6:4 to 8:2.
6. (Amended) A combination product as claimed in claim 2, in which the medicament (a) comprises a phosphatidyl glycerol.
7. A combination product as claimed in claim 6, in which the phosphatidyl glycerol comprises one or more diacyl phosphatidyl glycerols, of which at least a proportion of the acyl groups are unsaturated.
8. (Amended) A combination product as claimed in claim 2, in which the medicament (a) comprises one or more compounds selected from the group consisting of diacyl phosphatidyl cholines.

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9. A combination product as claimed in claim 8, in which the medicament (a) comprises dipalmitoyl phosphatidyl choline.

10. (Amended) A combination product as claimed in claim 2, in which the medicament (a) is in micronised form.

11. (Amended) A combination product as claimed in claim 2, in which said medicament (a) has a median particle size not exceeding 10µm.

12. A combination product as claimed in claim 11, in which said medicament (a) has a median particle size not exceeding 5µm.

13. A combination product as claimed in claim 12, in which said medicament (a) has a median particle size of less than 3 µm.

14. (Amended) A combination product as claimed in claim 2, in which the antiasthma drug comprises one or more respiratory drugs selected from the group consisting of β_2 -agonists, steroids, cromones, antimuscarinic drugs and leukotriene receptor antagonists.

15. (Amended) A combination product as claimed in claim 14, which comprises one or more of said antiasthma drugs in an amount of up to 10 parts by weight per hundred parts by weight of said first and second components of medicament (a) in combination.

16. (Amended) A combination product as claimed in claim 15, which comprises one or more of said respiratory drugs in an amount of up to one part by weight per hundred parts by weight of said first and second components of medicament (a) in combination.

17. (Amended) A combination product as claimed in claim 14, in which ingredient (b) comprises a β_2 -agonist.

18. (Amended) A combination product as claimed in claim 14, in which ingredient (b) comprises a steroid.

19. (Amended) A combination product as claimed in claim 14, in which ingredient (b) comprises a cromone.

20. (Amended) A combination product as claimed in claim 14, in which ingredient (b) comprises a leukotriene receptor antagonist.

21. (Amended) A combination product as claimed in claim 14, in which ingredient (b) comprises an antimuscarinic drug.

22. (Amended) A combination product as claimed in claim 2, in which at least ingredient (a) is arranged to be delivered to a patient in the form of at least one individual inhalable dose, the individual dose or each individual dose comprising said ingredient (a) in an amount of at least 10mg.

23. (Amended) A combination product as claimed in claim 22, in which the individual dose or each individual dose comprises said first and second components in a combined amount of at least 25mg.

24. (Amended) A combination product as claimed in claim 23, in which the individual dose or each individual dose comprises said ingredient (a) in a combined amount of at least 40mg.

25. (Amended) A combination product as claimed in claim 22, in which at least ingredient (a) is arranged for sequential delivery of a multiplicity of inhalable doses.

26. (Amended) A combination product as claimed in claim 1 or claim 2, in which the antiasthma drug is arranged for delivery in admixture with ingredient (a).

27. (Amended) A combination product as claimed in claim 1 or claim 2, in which the antiasthma drug is arranged for delivery separately from, and simultaneously or sequentially with, ingredient (a).

28. (Amended) A pack for use as part of a combination product according to claim 1 or claim 2, said pack including a delivery device for delivery of ingredient (a) to a patient and further comprising instructions to use said delivery device in a method of treatment including the separate simultaneous or sequential administration of an antiasthma drug.

29. (Amended) A method of prevention and/or treatment of asthma, comprising administering to a patient at least one dose of a combination product as defined in claim 1 or claim 2.

30. (Amended) A delivery device for administering to a patient by inhalation a medicament for the prevention and/or treatment of asthma, the delivery device containing a medicament comprising a surface active phospholipid (SAPL) composition in finely divided form, the SAPL composition including a component which enhances the spreading of the medicament, the delivery device being arranged for delivery of at least one individual dose of the SAPL composition in an amount of at least 10mg.

31. A delivery device for administering to a patient by inhalation a medicament for the prevention or treatment of asthma, the delivery device containing a medicament comprising a first component consisting of one or more phosphatidyl cholines and a second component consisting of one or more compounds selected from the group consisting of phosphatidyl glycerols, phosphatidyl ethanolamines, phosphatidyl serines, phosphatidyl inositols and chlorestyl palmitate, the delivery device being arranged for delivery of at least one individual inhalable dose, the or each individual dose comprising said first component and said second component in a combined amount of at least 10mg.

32. (Amended) A delivery device as claimed in claim 30, in which the medicament is as defined in claim 2.

33. (Amended) A delivery device as claimed in claim 30 or 31, which further includes means for dispensing an inhalable dose of an antiasthma drug.

34. (Amended) A medicament for use in the control of asthma, comprising (a) a surface active phospholipid (SAPL) composition in finely divided form conjointly with (b) an antiasthma drug.

35. A combination product for use in the prevention or treatment of asthma comprising

(a) a medicament comprising a first phospholipid component which is capable of binding to lung tissue and a second component which is capable of enhancing the spreading of said first component over an aqueous medium at 37°C, said medicament being in the form of a finely divided powder; and

(b) an antiasthma drug;

the ingredients (a) and (b) being arranged for administration in combination or separately, simultaneously or sequentially.

EXHIBIT B
PENDING CLAIMS

1. (Amended) A therapeutic combination product for use in the prevention and/or treatment of asthma comprising (a) a medicament comprising a surface active phospholipid (SAPL) composition in finely divided form, the SAPL composition including a component which enhances spreading of the medicament over a surface at about normal mammalian body temperature and (b) an antiasthma drug, wherein ingredients (a) and (b) are provided in a form for administration together or separately.
2. A combination product as claimed in claim 1, in which the ingredient (a) consists of a first component comprising one or more phosphatidyl cholines and a second component comprising one or more compounds selected from the group consisting of phosphatidyl glycerols, phosphatidyl ethanolamines, phosphatidyl serines, phosphatidyl inositols and chlorestyl palmitate.
3. A combination product as claimed in claim 2, in which medicament (a) comprises said first component and said second component in a weight ratio of from 1:9 to 9:1.
4. A combination product as claimed in claim 3, in which the proportion by weight of said first component exceeds that of said second component.
5. A combination product as claimed in claim 4, in which said first component and said second component are present in a weight ratio of from 6:4 to 8:2.
6. (Amended) A combination product as claimed in [any one of claims 1 to 5] claim 2, in which the medicament (a) comprises a phosphatidyl glycerol.
7. A combination product as claimed in claim 6, in which the phosphatidyl glycerol comprises one or more diacyl phosphatidyl glycerols, of which at least a proportion of the acyl groups are unsaturated.
8. (Amended) A combination product as claimed in [any one of claims 1 to 7] claim 2, in which the medicament (a) comprises one or more compounds selected from the group consisting of diacyl phosphatidyl cholines.
9. A combination product as claimed in claim 8, in which the medicament (a) comprises dipalmitoyl phosphatidyl choline.

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10. (Amended) A combination product as claimed in [any one of claims 1 to 9] claim 2, in which the medicament (a) is in micronised form.

11. (Amended) A combination product as claimed in [any one of claims 2 to 10] claim 2, in which said medicament (a) has a median particle size not exceeding 10µm.

12. A combination product as claimed in claim 11, in which said medicament (a) has a median particle size not exceeding 5µm.

13. A combination product as claimed in claim 12, in which said medicament (a) has a median particle size of less than 3 µm.

14. (Amended) A combination product as claimed in [any one of claims 1 to 13] claim 2, in which the antiasthma drug comprises one or more respiratory drugs selected from the group consisting of β₂-agonists, steroids, cromones, antimuscarinic drugs and leukotriene receptor antagonists.

15. (Amended) A combination product as claimed in [any one of claims 1 to 14] claim 14, which comprises one or more of said antiasthma drugs in an amount of up to 10 parts by weight per hundred parts by weight of said first and second components of medicament (a) in combination.

16. (Amended) A [delivery device] combination product as claimed in claim 15, which comprises one or more of said respiratory drugs in an amount of up to one part by weight per hundred parts by weight of said first and second components of medicament (a) in combination.

17. (Amended) A combination product as claimed in [any one of claims 1 to 16] claim 14, in which ingredient (b) comprises a β₂-agonist.

18. (Amended) A combination product as claimed in [any one of claims 1 to 16] claim 14, in which ingredient (b) comprises a steroid.

19. (Amended) A combination product as claimed in [any one of claims 1 to 16] claim 14, in which ingredient (b) comprises a cromone.

20. (Amended) A combination product as claimed in [any one of claims 1 to 16] claim 14, in which ingredient (b) comprises a leukotriene receptor antagonist.

21. (Amended) A combination product as claimed in [any one of claims 1 to 16] claim 14, in which ingredient (b) comprises an antimuscarinic drug.

22. (Amended) A combination product as claimed in [any one of claims 1 to 21] claim 2, in which at least ingredient (a) is arranged to be delivered to a patient in the form of at least one individual inhalable dose, the individual dose or each individual dose comprising said ingredient (a) in an amount of at least 10mg.

23. (Amended) A combination product as claimed in claim 22, in which the individual dose or each individual dose comprises said first and second components in a combined amount of at least 25mg.

24. (Amended) A combination product as claimed in claim 23, in which the individual dose or each individual dose comprises said ingredient (a) in a combined amount of at least 40mg.

25. (Amended) A combination product as claimed in [any one of claims 22 to 24] claim 22, in which at least ingredient (a) is arranged for sequential delivery of a multiplicity of inhalable doses.

26. (Amended) A combination product as claimed in [any one of claims 1 to 25] claim 1 or claim 2, in which the antiasthma drug is arranged for delivery in admixture with ingredient (a).

27. (Amended) A combination product as claimed in [any one of claims 1 to 26] claim 1 or claim 2, in which the antiasthma drug is arranged for delivery separately from, and simultaneously or sequentially with, ingredient (a).

28. (Amended) A pack for use as part of a combination product according to [any one of claims 1 to 27] claim 1 or claim 2, said pack including a delivery device for delivery of ingredient (a) to a patient and further comprising instructions to use said delivery device in a method of treatment including the separate simultaneous or sequential administration of an antiasthma drug.

29. (Amended) A method of prevention and/or treatment of asthma, comprising administering to a patient at least one dose of a combination product as defined in [any one of claims 1 to 27] claim 1 or claim 2.

30. (Amended) A delivery device for administering to a patient by inhalation a medicament for the prevention and/or treatment of asthma, the delivery device containing a medicament comprising a surface active phospholipid (SAPL) composition in finely divided form, the SAPL composition including a component which enhances the spreading of the medicament, the delivery device being arranged for delivery of at least one individual dose of the SAPL composition in an amount of at least 10mg.

31. A delivery device for administering to a patient by inhalation a medicament for the prevention or treatment of asthma, the delivery device containing a medicament comprising a first component consisting of one or more phosphatidyl cholines and a second component consisting of one or more compounds selected from the group consisting of phosphatidyl glycerols, phosphatidyl ethanolamines, phosphatidyl serines, phosphatidyl inositols and cholesteryl palmitate, the delivery device being arranged for delivery of at least one individual inhalable dose, the or each individual dose comprising said first component and said second component in a combined amount of at least 10mg.

32. (Amended) A delivery device as claimed in claim 30 [or claim 31], in which the medicament is as defined in [any one of claims 2 to 18] claim 2.

33. (Amended) A delivery device as claimed in [any one of claims 30 to 32] claim 30 or 31, which further includes means for dispensing an inhalable dose of an antiasthma drug.

34. (Amended) [Use of] A medicament for use in the control of asthma, comprising (a) a surface active phospholipid (SAPL) composition in finely divided form conjointly with (b) an antiasthma drug [in the manufacture of a medicament for the control of asthma].

35. A combination product for use in the prevention or treatment of asthma comprising

(a) a medicament comprising a first phospholipid component which is capable of binding to lung tissue and a second component which is capable of enhancing the spreading of said first component over an aqueous medium at 37°C, said medicament being in the form of a finely divided powder; and

(b) an antiasthma drug;

the ingredients (a) and (b) being arranged for administration in combination or separately, simultaneously or sequentially.

EXHIBIT C
REPLACEMENT SECTIONS

In the Section of the Application pertaining to "Cross-reference to Related Applications", the deletions and additions are as shown:

The present application is a nationalization of International Patent Application PCT/GB99/03952, filed November 26, 1999, which claims priority to British Patent Application 9912639.3, filed May 28, 1999 and to International Patent Application PCT/GB98/03543, filed November 26, 1998.

Field of the Invention

This invention relates to pharmaceutical products for use in the treatment of asthma and to delivery devices including the products.

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In the Section of the Application pertaining to "Cross-reference to Related Applications", the final text is as follows:

The present application is a nationalization of International Patent Application PCT/GB99/03952, filed November 26, 1999, which claims priority to British Patent Application 9912639.3, filed May 28, 1999 and to International Patent Application PCT/GB98/03543, filed November 26, 1998.

Field of the Invention

This invention relates to pharmaceutical products for use in the treatment of asthma and to delivery devices including the products.

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ABSTRACT

In the Section of the Application that forms the Abstract, the deletions and additions are as shown:

ABSTRACT

[A] Disclosed is a combination product for use in treating asthma and other respiratory conditions comprising a medicament comprising a surface active phospholipid composition in the form of a fine powder and an antiasthma drug. The product is arranged to be administered to the lungs by inhalation, for example, by [a device 1] the disclosed devices.

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ANTI-ASTHMATIC COMBINATIONS COMPRISING SURFACE ACTIVE PHOSPHOLIPIDS

This invention relates to pharmaceutical products for
5 use in the treatment of asthma and to delivery devices
including the products.

It has been estimated that asthma affects between 4 and
10 percent of the population, causing distress and alarm to
both sufferers and bystanders. Asthma attacks appear to be
10 precipitated in many cases by a number of factors such as
exercise or pollutants in the inspired air. Other agents
such as pollen and airborne particles may predispose an
asthma sufferer to an attack by sensitising the airways.
This has led to the belief that effective treatment should
15 include administration of drugs which reduce the sensitivity
of asthma sufferers to allergens or which neutralise the
allergic reaction.

The lungs and airways of non-asthmatics may contain a
natural protective barrier which prevents pollutants and
20 other potential irritants from reaching receptors which
would otherwise produce an acute attack. Studies have
suggested that it is possible to simulate in the lungs of
asthma sufferers the situation in normal lungs by causing
surface-active phospholipids (SAPL) to bind to the tissue
25 surface of the lungs, thereby reducing the number of
receptors exposed to noxious stimuli and reducing the
broncho-constrictor reflex.

SAPLs are used clinically for the treatment of
respiratory distress syndrome (RDS) in neonates. In this
30 role, it has been assumed that the SAPL functions by
reducing the high surface tension forces at the air-water
interface within the alveoli, thereby reducing the pressure
needed to expand the lungs, see Bangham et al., Colloids &

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Surfaces, 10 (1984), 337 to 341. Thus, commercially available formulations of SAPL have been designed to spread rapidly over an air-aqueous interface, thereby reducing what is otherwise a very high surface tension of water.

5 Limited clinical studies have been carried out to determine the effect of commercial SAPLs marketed for treatment of RDS in neonates on asthmatic subjects, - see Kurashima et al Jap. J. Allergol 1991; 40, 160. This paper reported some amelioration of bronchoconstriction in
10 asthmatic adults using an SAPL obtained by extraction from bovine lungs. In another study on children, also using an SAPL obtained from bovine lungs, no significant changes in lung function or histamine response were found, - see Oetomo et al - American Journal of Respiratory and Critical Care
15 Medicine 153; 1996, page 1148.

EP 0 528 034A describes the use of pulmonary surface active material as an ingredient of an antiasthmatic, which is in the form of a liquid or suspension for injection or spraying into the patient's air way.

20 The invention provides a therapeutic combination product for use in the prevention and/or treatment of asthma comprising

(a) a medicament comprising a surface active phospholipid (SAPL) composition in finely divided form, the
25 SAPL including a component which enhances spreading of the medicament over a surface at about normal mammalian body temperature; and

b) an antiasthma drug;
wherein ingredients (a) and (b) are provided in a form for
30 administration together or separately.

It is believed that the finely divided powder of ingredient (a), which preferably comprises at least first and second components, has two important effects:-

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First, the medicament (a) has surfactant properties, which enable it to spread rapidly over the surfaces of the lungs and air passages. It is an important feature of the present invention that the medicament (a) is in the form of a powder, that is, it is in solid form. The "dry" surfactant has a high surface activity. It is believed that, on contact of a first component of the medicament (a) with the mucous within the lungs, the presence of a second component results in a lowering of the melting point of the first component, promoting rapid spreading of the first component over the liquid-air interface as a thin film at body temperature. For example, the normal melting temperature of dipalmitoyl phosphatidyl choline, which is a preferred first component, is about 40°C, that is, above the normal body temperature. When used in combination with a suitable second component, such as a phosphatidyl glycerol, however, the melting point of the dipalmitoyl phosphatidyl choline can in effect be reduced to below the normal body temperature.

Second, once the surface active medicament is in situ over the surfaces of the lungs and air passages, a component of the composition is thought to migrate across the mucous layer enabling a thin hydrophobic lining or coating to be adsorbed onto the tissue surface. Thus, over and above the surface tension reducing properties mentioned above, the medicament of the invention is believed to provide a protective effect by virtue of the adsorbed layer. In binding to the epithelium, the phospholipid may mask the irritant receptors which elicit the bronchoconstrictor reflex, that is, which cause narrowing of the bronchi.

The medicament (a) is in finely divided solid form. It is believed that, as a consequence of the high surface activity of medicament (a) in that form there results a

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significant drop in surface tension on contact with the aqueous mucous layer of the lung, giving enhanced effectiveness of ingredient (a) and permitting improved access to the lung surfaces for the antiasthma drug(s) to be administered. Thus, the use of the medicament (a) in combination with an antiasthma drug is believed to enhance the effectiveness of the antiasthma drug.

Moreover, as mentioned above, the binding of the phospholipid component to the lung surface is believed to reduce bronchostriction as a consequence of a reduction in receptor-mediated activity attributable to the masking of irritant receptors. That reduced bronchostriction acts cumulatively with the anti-bronchostrictive activity of the antiasthma drug. Thus, in some circumstances it may be possible for dosages of an antiasthma drug to be administered to a given patient to be reduced, as a consequence of the synergistic effect of medicament (a) in enhancing the effectiveness of the antiasthma drug as well as the additional anti-bronchostrictive activity of medicament (a) itself.

"Finely divided" as used herein means that the material has a particle size distribution which is such that at least a major proportion by weight of the particles are small enough to enter into a patient's airways and, preferably, deep into the lungs when inhaled. In practice, the first and second components preferably each have a particle size distribution which is such that not less than 90%, by weight, of the particles of those components in combination, and more preferably of each of the first and second components, have a particle size of not greater than $10\mu\text{m}$, and especially of not greater than $5\mu\text{m}$. Advantageously, the median particle size of the combined first and second components, and more preferably of each of the first and

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second components is not more than $10\mu\text{m}$, and preferably not more than $5\mu\text{m}$. The median particle size may be less than $3\mu\text{m}$, for example, about $1.2\mu\text{m}$. It may be desirable in some circumstances for the particles to have a median particle size of at least $0.5\mu\text{m}$. The size of the particles may be calculated by laser diffraction, or by any other method by which the aerodynamic diameter of particles can be determined. "Median particle size" as used herein means mass median aerodynamic diameter ("MMAD"). The MMAD may be determined using any suitable method, for example, using a Multi-Stage Liquid Impinger in accordance with the method described in European Pharmacopoeia (supplement 1999) 2.9.18 (Aerodynamic assessment of fine particles). Alternatively, the size distribution of the particles may be characterised by their volume mean diameter (VMD). Advantageously, the VMD is not more than $10\mu\text{m}$, for example not more than $5\mu\text{m}$, and preferably less than $3\mu\text{m}$. Finely divided dry powders of this kind (which may be described as fumed powders) can be adsorbed onto the surfaces of lung tissue and are believed, in use, to become bound to the epithelium.

A finely divided solid mixture of said first and second components of the medicament (a) may be obtained by size reduction of larger particles by any suitable size reduction method, preferably before mixing. Preferably, the first component of the medicament (a) comprises one or more compounds selected from the group consisting of diacyl phosphatidyl cholines. Examples of suitable diacyl phosphatidyl cholines (DAPCs), are dioleoyl phosphatidyl choline (DOPC); distearyl phosphatidyl choline (DSPC) and dipalmitoyl phosphatidyl choline (DPPC). Each of those compounds appears to be capable of forming a thin film or coating on surfaces of the lungs. Most preferably, the first component is DPPC.

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The second component may comprise one or more compounds selected from the group consisting of phosphatidyl glycerols (PG); phosphatidyl ethanolamines (PE); phosphatidyl serines (PS); phosphatidyl inositols (PI) and chlorestyl
5 palmitate (CP).

Phosphatidyl glycerol (PG) is believed to be capable of binding to lung tissue and possibly enhancing the binding of the first component and is, therefore, a preferred second component. PG is also a preferred second component because
10 of its ability to form with the first component a very finely-divided, dry powder dispersion in air.

The medicament advantageously comprises a diacyl phosphatidyl choline and a phosphatidyl glycerol. The phosphatidyl glycerol is advantageously a diacyl
15 phosphatidyl glycerol. The acyl groups of the phosphatidyl glycerol, which may be the same or different, are advantageously each fatty acid acyl groups which may have from 14 to 22 carbon atoms. In practice, the phosphatidyl glycerol component may be a mixture of phosphatidyl
20 glycerols containing different acyl groups. The phosphatidyl glycerol is expediently obtained by synthesis from purified lecithin, and the composition of the acyl substituents is then dependent on the source of the lecithin used as the raw material. It is preferred for at least a
25 proportion of the fatty acid acyl groups of the phosphatidyl glycerol to be unsaturated fatty acid residues, for example, mono- or di- unsaturated C18 or C20 fatty acid residues. Preferred acyl substituents in the phosphatidyl glycerol component are palmitoleoyl, oleoyl, linoleoyl, linolenoyl
30 and arachidonoyl. The medicament preferably comprises dipalmitoyl phosphatidyl choline and phosphatidyl glycerol, with the phosphatidyl moiety of the phosphatidyl glycerol

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advantageously being obtainable from the phosphatidyl moiety of egg lecithin.

The first and second components of the medicament (a) may be present in a weight ratio of from 1:9 to 9:1.

- 5 Advantageously, the proportion by weight of the first component exceeds that of the second component. Preferably, said first component and said second component are present in a weight ratio of from 6:4 to 8:2. At a weight ratio of about 7:3, the mixture spreads rapidly at a temperature of
10 35°C or above.

DPPE can be prepared synthetically by acylation of glycerylphosphorylcholine using the method of Baer & Bachrea - Can. J. Of Biochem. Physiol 1959, 37, page 953 and is available commercially from Sigma (London) Ltd. The PG may
15 be prepared from egg phosphatidylcholine by the methods of Comfurions et al, Biochem. Biophys Acta 1977, 488, pages 36 to 42; and Dawson, Biochem J. 1967, 102, pages 205 to 210. When co-precipitated with DPPE from a common solvent such as chloroform, PG forms with DPPE a fine powder which spreads
20 rapidly over the surfaces of the airways and lungs. The most preferred composition of the invention contains DPPE and a phosphatidyl glycerol derived from egg phosphatidyl choline and having a mixture of C16, C18 (saturated and unsaturated) and C20 (unsaturated) acyl groups. One form of
25 that composition is obtainable from Britannia Pharmaceuticals Ltd., 41-51 Brighton Road, Redhill, Surrey, under the trade mark "ALEC". For use in the device of the present invention, however, it is preferred for the particle size of the mixture to be less than that of "ALEC" in the
30 form in which it is currently obtainable commercially. To obtain a mixture in which the particle size is suitable for use in the device of the invention, the phospholipid components may be dissolved in a suitable solvent, for

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example ethanol, the solution filtered and vacuum-dried, and the solid product size-reduced to obtain particles of the desired size. During size-reduction, care should be taken to protect the mixture from moisture, oxygen, direct heat,
5 electrostatic charge and microbial contamination.

"Antiasthma drug" is used herein to include any drug which has biological activity against asthma. It will be appreciated that, as used herein, "antiasthma drug" is to be understood as not including the compositions of the
10 medicament of ingredient (a). The antiasthma drug may comprise one or more respiratory drugs including but not limited to drugs selected from the group consisting of β_2 -agonists, steroids, cromones, antimuscarinic drugs and leukotriene receptor antagonists. The combination product
15 may comprise one or more said antiasthma drugs in an amount of up to 10 parts, especially up to one part by weight per hundred parts by weight of said first and second components, in combination, of the said medicament (a). It will be appreciated that the respiratory drug or drugs should be
20 present in such an amount that each dose delivered by the device contains an effective amount of the drug or drugs.

The combination product may comprise a β_2 -agonist which may be terbutaline, a salt of terbutaline, for example terbutaline sulphate, or a combination thereof or may be
25 salbutamol, a salt of salbutamol or a combination thereof. Salbutamol and its salts are widely used in the treatment of respiratory disease. The active particles may be particles of salbutamol sulphate. Long-acting β_2 adrenoceptor agonists may be present, for example, formoterol,
30 salmeterol, and salts thereof.

The combination product may comprise an antimuscarinic drug, for example ipatropium bromide.

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The combination product may comprise a steroid, which may be, for example, beclomethasone dipropionate, budesonide, triamcinolone acetonide or may be fluticasone. The medicament may comprise other prophylactic drugs, including cromones, for example, sodium cromoglycate or nedocromil. The medicament may include a leukotriene receptor antagonist.

Advantageously, at least ingredient (a) is arranged to be delivered to a patient in the form of at least one individual inhalable dose, the or each individual dose comprising said first and second components of ingredient (a) in a combined amount of at least 10mg. Whereas phospholipids have been disclosed previously as adjuvants in certain forms of delivery device, the amounts of phospholipid administered in a dose by those previously disclosed devices have been much smaller than those envisaged according to the present invention. In fact, it is preferred in accordance with the present invention for each individual dose to comprise at least 25mg, and more especially at least 40mg of said first and second components. The first and second components are substantially non-toxic, and the upper limit of the dosage of ingredient (a) may therefore in general be selected having regard to convenience taking into account matters such as, for example, the comfort of the patient and/or design parameters of the device. In general, however, the device will be such that it can deliver doses of up to 1000mg, advantageously up to 500mg, preferably up to 200mg, and especially up to 100mg. Preferably, at least ingredient (a) is arranged for sequential delivery of a multiplicity of inhalable doses.

The products of the invention have the further advantage that the first and second components of the

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medicament (a) may be of synthetic origin. It has been found undesirable to expose asthmatic patients to proteins of animal origin, because such proteins can have a sensitising effect on such patients, and thus the use of synthetic material has considerable advantages over the use of surfactants of animal origin that may contain animal protein.

Because it is desirable in the present invention to achieve a relatively long term adsorption of the medicament (a) on the lung surface, it is highly desirable that the medicament (or any active components) should not break down in the environment of the lungs. One of the factors which will reduce the life of a lining or coating will be the presence of enzymes, such as phospholipase A, capable of digesting DPPC and/or PG. Such enzymes only attack the laevorotatory (L) form, which constitutes the naturally occurring form. Therefore, the medicament should preferably contain the dextrorotatory (D) form or at least comprise a racemic mixture, which is obtained by synthetic routes. Suitable dispersion devices may employ a propellant such as a halocarbon to form the gas stream and may include a tapered discharge nozzle baffle or a venturi to accelerate particles through a discharge nozzle, and to remove oversized particles. Suitable halocarbons include hydrofluorocarbons, hydrofluorochlorocarbons and fluorochlorocarbons having a low boiling point, such as those marketed under the trade mark "Freon". The medicament may be packaged with a propellant in a pressurised aerosol container within the inhaler. Other inhalers have an impeller which mixes the powder into an air stream and delivers the powder-laden air into the patient's airways - see, e.g. US 5,577,497.

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- A preferred method and apparatus for administering the medicament (a) involves dispersing the powdered medicament in a propellant gas stream. For example, a pressurised canister of a liquefied gas may be connected to a vial containing the medicament. By releasing controlled amounts of gas from the canister into the vial, increments of the medicament are ejected from the vial as a cloud of powder and may be inhaled by the user. Where compatible with the characteristics of the antiasthma drug to be co-administered, that drug may be introduced into the gas stream, so that it is administered in admixture with the medicament (a). It is envisaged that, in use, one or two inhalable doses of the medicament (a), each dose containing 50mg, may be administered up to three times daily.
- Where the antiasthma drug is to be administered separately and sequentially with the medicament (a) administration of the antiasthma drug may occur as and when required by the patient and the timing of administration may thus be independent of the timing of administration of the medicament (a).
- The present invention provides a delivery device for administering to a patient by inhalation a medicament for the prevention or treatment of asthma, the delivery device containing a medicament comprising a surface active phospholipid (SAPL) composition in finely divided form, the SAPL including a component which enhances the spreading of the medicament and the delivery device being capable of delivering of at least one individual dose in an amount of at least 10mg.
- The invention also provides a delivery device for administering to a patient by inhalation a medicament for the prevention or treatment of asthma, the delivery device containing a medicament, the medicament being in finely

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divided powder form and comprising a first component consisting of one or more phosphatidyl cholines and a second component consisting of one or more compounds selected from the group consisting of phosphatidyl glycerols, phosphatidyl
5 ethanolamines, phosphatidyl serines, phosphatidyl inositols and chlorestyl palmitate, the delivery device being arranged for delivery of at least one individual inhalable dose, the or each individual dose comprising said first phospholipid component and said second component in a combined amount of
10 at least 10mg.

Furthermore, the invention provides use of (a) a surface active phospholipid (SAPL) composition in finely divided form conjointly with (b) an antiasthma drug in the manufacture of a medicament for the control of asthma.

15 One form of dispenser according to the invention will now be described in detail, by way of illustration, with reference to the accompanying drawings, in which:

- Fig. 1 is a side elevation of a delivery device;
20 Fig. 2 is a similar view, but shows its interior; and
Fig. 3 is a schematic view of another embodiment of delivery device in accordance with the invention.

In the drawings, a casing 1 is formed from two plastic
25 mouldings 2 and 3 which snap together to form a container for a pressurised canister 4 and a vial 5. Canister 4 contains a low boiling liquid, preferably a hydrofluorocarbon such as HFA-134a or HFC-227, under sufficient pressure to maintain the propellant liquid at
30 normal room temperature. Vial 5 contains the powdered medicament (a), such as "ALEC". Canister 4 has a release valve 6 which is received in a recess 7 so that finger pressure on the inverted end 8 of the canister will cause

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propellant to be released into a tube 9. Tube 9 is typically a hard plastics, e.g. pvc or polypropylene, tube of about 2-3mm outside diameter and about 0.5 to 2mm inside diameter. Tube 9 connects valve 6 with a fitting 10 and
5 thence to a tube or needle 11 which extends into the vial 5. Vial 5 may be closed with a rubber seal which is penetrated by the tube or needle 11 and self-seals around the tube or needle. A second needle or tube 12 extends part way into the vial through the rubber seal in the neck of the vial and
10 connects with a fitting 13. Fitting 13 discharges into a mouthpiece 14 which is a comfortable shape for the user to place in the mouth. When the patient is in need of medication, he places the mouthpiece 14 into his mouth and breaths and simultaneously depresses the canister 4. This
15 causes a cloud of medicament to be dispensed into the patient's airways. Fittings 10 and 13 may be valves. Valves 10 may be set to permit measured quantities of propellant to enter the vial. Similarly, valve 13 may be set to release when the pressure in the vial reaches a
20 predetermined level. It will be appreciated that the dispenser can be used one-handed in an analogous manner to a conventional nebulizer.

The antiasthma drug may be administered separately from a separate device either immediately before or after
25 administration of the medicament (a), or separately as required by the patient. The antiasthma drug may be dispensed from any suitable form of inhaler device, such as a dry powder inhaler or pressurised metered dose inhaler. Such devices containing antiasthma drugs are well known and
30 widely available commercially, and do not require further explanation.

Instead, in addition to the powdered phospholipid composition, the vial 5 may incorporate other known

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pulmonary or respiratory medicaments such as salbutamol, Beclomethasone, corticosteroids, or other asthma drugs. It is, however, preferred to package the conventional asthma drug in the propellant canister or in a capsule interposed
5 between the propellant container and the vial containing the phospholipid composition. In this way, the lungs and airways receive a cloud of phospholipid composition and an aerosol of the conventional drug sequentially or simultaneously. This combined therapy gives both quick
10 relief and lasting protection as the film of phospholipid composition spreads over the lung tissue. Instead of packaging the phospholipid composition in a multi-use vial, it may be contained in a capsule, which may be a single use quantity, between the outlet from the propellant canister
15 and the mouthpiece.

Another form of delivery device is illustrated in Fig. 3.

Conceptually, the device 101 shown in figure 3 provides a receptacle 102 having a volume of several litres which is
20 filled with aerosolubilized solid SAPL composition, optionally also including an antiasthma drug, and is then inhaled by a patient via a breathing tube 120 connected to a pipe 104 leading from the receptacle. Receptacle 102 is first evacuated using vacuum pump 115. A quantity of the
25 solid, powdered SAPL composition is contained within a mesh type holder 105 within a tube 106, and air is then introduced through the tube 106 to cause the SAPL powder to form an aerosolubilized cloud within the receptacle 102. When receptacle 102 reaches approximately atmospheric
30 pressure, breathing tube 120 is opened to permit the patient to inhale the SAPL composition.

The device 101 comprises a stainless steel receptacle 102 of volume approximately 4 litres which has an aperture

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103 at its top extremity to which a vertically extending pipe 104 is connected. Pipe 104 is connected to a transverse pipe 109 and also a breathing tube 120 which extends through a screen 121, so that the apparatus is not visible to the patient. Breathing tube 120 may be fitted with a plug at its distant end, the plug being removable before use. A mesh holder 105 is mounted on the top of the receptacle 102 as part of a connection between an air line 106 and the receptacle. The mesh holder can be disassembled to introduce a quantity of powdered medicament into the delivery device. One end of the air line 106 is connected, via the mesh holder, to the receptacle 102 via a port 103. The other end of the air line 106 is connected, via control device 107, to a regulated source 108 of compressed propellant, e.g. air. If desired, the source of compressed propellant can also contain a biologically active component for the treatment of asthma. The pipe 104 extends upwardly from receptacle to meet a horizontally extending pipe 109, from one end of which there extends pipe 110 to atmosphere. A valve 111, openable by means of a handle 112, is provided in the horizontally extending pipe 109, closing off the pipe 110 from the receptacle 102 except when valve 111 is open.

At the other end of the horizontal pipe 109 there is provided a pressure gauge 113. At that end, the horizontal pipe 109 is connected to an air line 114, which extends, via the control device 107, to a vacuum pump 115, which is controllable independently of the control device 107. A valve 116, operable by a handle 117, is provided for the purpose of opening or closing the pipe between the receptacle 102 and the air line 114.

A safety pressure relief valve 118 is incorporated in the apparatus and is preferably arranged to open at 0.034 bar above atmospheric pressure.

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In use, micronised SAPL composition (optionally together with an antiasthma drug) may be introduced into the mesh holder device 105, which is then inserted into the port 103 leading into the receptacle 102. On insertion of the mesh holder device, the receptacle is sealed, the valves 111 and 116 both being closed. The pressure inside the receptacle 102 is then reduced by means of opening valve 116 and pumping air out of the receptacle 102 through air line 114.

Control unit 107 may include a needle valve (which may be adjustable) to control the rate at which air is evacuated from the receptacle 102. If pressure falls too rapidly in the receptacle, it may cause the powdered medicament in the mesh holder device to be sucked prematurely into the receptacle. Thereafter, the valve 116 is closed. Whilst the receptacle 102 remains sealed at reduced internal pressure, the regulated compressed air source 108 is actuated temporarily to inject air into the receptacle 102 through the mesh holder device 105. As a consequence, the powder in the mesh holder device 105 becomes aerosolised and enters the receptacle 102. The pressure may be monitored using the pressure gauge 113 and should at this stage be at or slightly below atmospheric pressure.

The plug is then removed from the mouthpiece of the breathing tube and the patient can then inhale the contents of the receptacle by sucking on the mouthpiece end of the breathing tube.

After the inhalation step, the valve 111 may be closed, and the cycle recommenced.

If desired, the quantity of the powder successfully aerosolised may be determined by weighing the mesh and powder before use (the weight of the mesh previously having

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been determined) and weighing the mesh with any residual powder after use of the device.

As indicated above, an antiasthma drug may be present in the source of compressed propellant, or be placed in the mesh holder device with the SAPL.

If preferred, or if necessitated by the nature of the antiasthma drug to be administered in a combination treatment with the surface active phospholipid composition, the antiasthma drug may be administered separately from another device, for example, a dry powder inhaler or pressurised metered dose inhaler of known kind widely available for the administration of antiasthma drugs.

Determination of fine particle fraction of phospholipid composition

As already mentioned, finely divided ALEC for use in the products of the invention may be obtained by dissolving, filtering and vacuum-drying the components and size-reducing the solid product so obtained. The delivery of the size-reduced material was monitored using a Multi-Stage Impinger (MLSI) in accordance with the method described in European Pharmacopoeia (supplement 1999), 2.9.18 (Aerodynamic assessment of fine particles). Vials of the material were loaded on the 5-stage MLSI and delivery of the material tested under a number of operating conditions. Each volume of air drawn of 4l is considered equivalent to one patient inhalation. The results, in Table 1, showed that a relatively large respirable fraction was generated. The respirable (or fine particle) fraction represents particles which reach stages 3, 4 and 5 of the MLSI, indicating a particle size of less than about 5.3µm. Such particles are considered to be of a size such that they would enter deep into the lung of a typical patient.

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Table 1.

Flow Rate Through MSLI (L/min)	Volume of Air Drawn (Litres)	Total Mass of Phospho-lipid Loaded	Mass Delivered into Device (mg) (% of mass loaded)	Mass of Phospho lipid MSLI (mg)	Fine Particle Fraction (mg)	Fine Particle Fraction (% ex-device)
100	4L	179.1	150.3 (84%)	55.1	46.5	84.5
100	2 x 4L	169.2	132.5 (78%)	60.0	45.1	75.1
100	3 x 4L	162.0	133.1 (82%)	66.0	55.7	84.4
100	3L	136.1	119.8 (88%)	58.6	45.1	76.9
100	4L	129.7	107.9 (83%)	53.0	44.7	84.3
100	2 x 4L	113.5	94.0 (83%)	46.1	37.6	81.7
100	4 x 4L	387.6	340.4 (88%)	117.5	86.5	73.6

Determination of surface activity of phospholipid

5 compositions

A 2cm x 2cm platinized grey dipping plate is heated to cherry red using the flame from a Bunsen burner or similar torch. The plate is suspended from an electronic balance capable of weighing up to 500mg.

- 10 To calibrate the apparatus, a small teflon dish is filled with distilled water at approximately 20°C (room temperature) and placed on a laboratory jack just beneath the dipping plate. The dish is then raised so that the dipping plate just breaks the surface of the water, evenly
- 15 along the bottom edge. The meniscus drawn up the dipping plate is used to set the display of the pen recorder of the electronic balance to read about 73 mNm^{-1} the air/water surface tension of water at 20°C). The Teflon dish is lowered, emptied, cleaned, dried and then filled with
- 20 reagent grade methanol. The dipping plate is cleaned as described above. The dish is then raised so that the dipping plate just breaks the surface of the methanol, evenly along the bottom edge. The meniscus drawn up the

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dipping plate will cause the pen recorder to read about 22mNm^{-1} (the air/methanol surface tension of methanol at 20°C^1). The Teflon dish is lowered and the dipping plate is cleaned as described above. A zero-reading should be
5 obtained for the cleaned plate alone (i.e. suspended in air).

To obtain a quantitative measure of the surface activity of a material, the Teflon dish is warmed to about 37°C , filled with water at not more than 37°C and placed on
10 a laboratory jack just beneath the cleaned plate. The dish is then raised so that the dipping plate just breaks the surface of the water, evenly along the bottom edge. The meniscus drawn up the dipping plate will give a reading of about 70mNm^{-1} (the approximate air/water surface tension of
15 warm water). The material is applied onto the surface of the water using a small spatula. The amount applied should be sufficient to ensure that a complete monolayer has been formed on the surface of the water, such that an excess (as small free-floating particles) can be observed. The surface
20 tension should fall instantly, that fall being recorded by the pen recorder. Equilibrium surface tension readings are taken from the pen recorder after about 1 minute. The temperature of the water in the Teflon dish should be not less than 35°C immediately after the reading is taken.

25 The term "high surface activity" as used herein with reference to any composition for use in accordance with the invention means that the equilibrium surface tension, as measured in the above method, is at least 10% lower than the surface tension before the composition is applied to the
30 water surface. In practice, the reduction in surface tension obtainable using certain phospholipid compositions such as those mentioned above in illustration of medicament (a) may exceed 50%.

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A component included in admixture with another material is to be understood as enhancing the spreading of the other material if, in carrying out the above method for determination of surface activity using the mixture and, separately, using the other material alone, the time taken for the equilibrium surface tension to be reached is shorter for the mixture, as compared to the material alone.

The above method describes determination of surface activity at 37°C. It will be appreciated that, where reference is made herein to enhancing spreading at about normal mammalian body temperature, the method should be carried out at about the normal body temperature of the relevant mammal, where that is not about 37°C.

The following Example illustrates the binding of a preferred phospholipid to the epithelium:

Example

Reagents

L- α -Phosphatidylcholine, 1,2-di[1-¹⁴C]palmitoyl in Toluene:Ethanol (1:1 v/v), 114mCi/mmol, 50 μ Ci in 2mL (CFA604 B36, Amersham)

L- α -Phosphatidylcholine, dipalmitoyl (C16:0) (P-6267, Sigma)

DL- α -Phosphatidyl-DL-glycerol, dipalmitoyl (C16:0) (P-5650, Sigma)

Egg Phosphatidylglycerol (Batch 24756, Macfarlan Smith, Ltd.)

Sodium Chloride, 0.9%, B.P. (Baxter Healthcare)

Calcium Chloride (C-4901, Sigma)

Toluene (T-4428, Sigma)

Ethanol, AnalaR (10107.7Y, BDH)

NCS-II Tissue Solubilizer, 0.5N Solution (NNCS-502), Amersham)

OCS Organic Counting Scintillant (NOCS104, Amersham)

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In preparation for the dispersions in which the epithelium would be incubated, stock solutions of the phospholipid components were prepared on the first day of Run 1. These solutions were as follows:

5

L- α -DPPC, 2.4mg. mL⁻¹ in toluene:ethanol, 1:1

DL- α -DPPG, 3.0mg. mL⁻¹ in toluene:ethanol, 1:1

Egg PG, 3.0mg. mL⁻¹ in toluene:ethanol, 1:1

- 10 All of the above solutions were stored at 4°C in glass vials, the threads of which were sealed with teflon tape to minimise evaporation of the solvent. Each glass vial was then placed inside a second, tightly capped glass vial. These solutions were used for each of the five runs in the
- 15 trial. A solution of 200mg. L⁻¹ CaCl² in 0.9% saline was also prepared on the first day of Run 2 and was used in each of Runs 2 to 5.

Equipment

- 20 Special Ultrasonic Cleaner, Model G112 SPLG (Laboratory Supplies Co. Inc., Hicksville, N.Y., U.S.A.)
- VF2 Vortex (IKA-Labortechnik)
- Shaking Water Bath, Model TSB2-201-A (Thermoline Scientific Equipment, Smithfield, Australia)
- 25 Contherm Series Five, Fan Forced Oven (Contherm Scientific Ltd. Lower Hutt, N.Z.) TRI-CARB 2700TR Liquid Scintillation Analyser (Packard Instrument Co., Meriden, CT, U.S.A.)
- Ultrasonic Cleaner, Model FXPI2 (Unisonics Pty. Ltd. Sydney, Australia)

30

Bronchial Epithelium

To provide a source of bronchial epithelium, porcine lungs were obtained from an abattoir within 24h of death. The

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- lungs had been stored at 4°C since the time of death. The secondary bronchus was dissected from the right and/or left lungs. The exterior surface of the bronchus was trimmed of all lung tissue, and the bronchus was further cut into
- 5 sections having a known surface area of bronchial epithelium (approximately 0.5cm x 0.5cm), leaving the epithelium and cartilage intact. The surface of the epithelium was rinsed with 0.9% saline to remove any mucus.
- 10 Where necessary sections of bronchial epithelium were stored in 0.9% saline at -20°C for 3 to 7 days until required for use. The sections were thawed before use on the first day of each run.
- 15 For bronchial epithelium, a total of five runs were completed. Each run consisted of three groups, as follows:
1. DPPC only
 - 20 2. DPPC + DPPG
 3. DPPC+eggPG

Four dispersions were prepared on the first day of each run. All groups received both 20.5µL (3.3µg) of ¹⁴C-L-α-DPPC and

25 5.5µL (13.2µg) of unlabelled L-α-DPPC from the stock solutions. In addition, Group 2 received 5.5µL (16.5µg) DL-α-DPPG, while the same quantity of egg PG was added to Group 3. In Groups 2 and 3, the ratio of total DPPC to PG was 1:1. The phospholipid component was mixed with 6.6ml of

30 0.9% saline for Groups 1, 2, and 3. All of the above listed volumes were used when there were two sections of epithelium in each treatment group. When the number of sections was increased, the volumes of all components were increased

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accordingly, keeping all quantities in the same proportions as above. Table 2 summarises the additives to the incubation mixtures.

5 Table 2. Components of Incubation Dispersions

Group	Saline	¹⁴ C-L- α -DPPC	L- α -DPPC	DL- α -DPPC	Egg PG
1	X	X	X		
2	X	X	X	X	
3	X	X	X		X

To solubilise the phospholipid components in the aqueous medium, each of the four incubation dispersions was
10 sonicated for 45min, then vortexed to mix for 1min.

From each dispersion, two lots of 2.8mL were transferred to two glass vials. A single section of epithelium was incubated in each of these dispersions, so that there were four groups of two sections of bronchial
15 epithelium in each group. Bronchial epithelium was taken from a single pig on any given day of incubation. Incubation was at 37°C for 24h in a shaking water bath.

Aliquots of the Group 1 dispersion were transferred to glass scintillation vials and incubated at 37°C in an oven
20 for the 24h. These aliquots were used as the standards for the calibration curve. Matching aliquots from the other group dispersions were also taken, and the β -counts from these were compared with those from the group 1 dispersion as a check that all dispersions contained the same quantity
25 of DPPC.

On the second day of each run, the sections of epithelium were removed from the incubation dispersions and were each rinsed 20 times with 0.9% saline, warmed to 37°C

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in a water bath, to remove any loosely adhering phospholipid. Care was taken not to mechanically disturb the mucosal surface of epithelium. Each section of bronchial epithelium was then removed from the attached cartilage. The sections of epithelium were further cut into smaller pieces to aid the digestion of the tissue by the solubilising agent which was added in a volume of 1 .5mL to the epithelium in scintillation vials. The same volume of solubiliser was added to each of the standard aliquots and to a blank. All vials were gently shaken to mix the contents and were warmed to 55°C in a fan-forced convection oven overnight (18-20h).

On the third day of each run, 10mL of organic counting scintillant were added to each scintillation vial, and these were vortexed to mix for 30s.

The β -counts of each sample and standard were measured using a liquid scintillation analyser. A second count was conducted within 7h of the first count. If the two counts were similar, only the first count was used to construct the line of calibration and to quantify the samples.

From the line of calibration, the mass of ^{14}C -DPPC adsorbed to each section of epithelium was calculated. To calculate the mass of total DPPC adsorbed to each section, the mass of ^{14}C -DPPC was multiplied by 5 since the quantity of ^{14}C -DPPC in each of the dispersions was 1/5 of the total amount of DPPC. The result is expressed in Table 2 as the total amount of DPPC adsorbed per cm^2 of epithelium.

The results in Table 3 show that increased binding of DPPC to bronchial epithelium is observed in the presence of DPPG, but that the extent of binding is improved still further where Egg PG is used instead of DPPG.

While the present invention has been described with particular reference to the treatment of human patients for

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asthma, it is possible that the invention may also be applicable to the treatment of other pulmonary diseases or conditions such as rhinnitis.

The combination product of the present invention
 5 may also be employed in the treatment of pulmonary conditions in other mammals. An example is reactive airway disease in horses.

Table 3.

10 Total DPPC Adsorbed to Bronchial Epithelium ($\mu\text{g}/\text{cm}^2$)

	DPPC	DPPC:DPPG, 1:1	DPPC:Egg PG, 1:1
	0.341	0.501	0.878
	0.299	0.321	0.743
15	0.219	0.214	0.472
	0.116	0.263	0.731
	0.276	0.378	0.705
	0.280	0.494	0.529
	0.528	0.355	0.836
20	0.192	0.419	0.792
	0.340	0.294	0.986
	0.321	0.362	0.791
n	10	10	10
25 Mean	0.291	0.360	0.746
SD	0.110	0.093	0.153

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Claims

1. A therapeutic combination product for use in the prevention and/or treatment of asthma comprising (a) a medicament comprising a surface active phospholipid (SAPL) composition in finely divided form, the SAPL including a component which enhances spreading of the medicament over a surface at about normal mammalian body temperature and (b) an antiasthma drug, wherein ingredients (a) and (b) are provided in a form for administration together or separately.
2. A combination product as claimed in claim 1, in which the ingredient (a) consists of a first component comprising one or more phosphatidyl cholines and a second component comprising one or more compounds selected from the group consisting of phosphatidyl glycerols, phosphatidyl ethanolamines, phosphatidyl serines, phosphatidyl inositols and chlorestyl palmitate.
3. A combination product as claimed in claim 2, in which medicament (a) comprises said first component and said second component in a weight ratio of from 1:9 to 9:1.
4. A combination product as claimed in claim 3, in which the proportion by weight of said first component exceeds that of said second component.
5. A combination product as claimed in claim 4, in which said first component and said second component are present in a weight ratio of from 6:4 to 8:2.
6. A combination product as claimed in any one of claims 1 to 5, in which the medicament (a) comprises a phosphatidyl glycerol.
7. A combination product as claimed in claim 6, in which the phosphatidyl glycerol comprises one or more diacyl phosphatidyl glycerols, of which at least a proportion of the acyl groups are unsaturated.

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8. A combination product as claimed in any one of claims 1 to 7, in which the medicament (a) comprises one or more compounds selected from the group consisting of diacyl phosphatidyl cholines.

5 9. A combination product as claimed in claim 8, in which the medicament (a) comprises dipalmitoyl phosphatidyl choline.

10 10. A combination product as claimed in any one of claims 1 to 9, in which the medicament (a) in micronised form.

11. A combination product as claimed in any one of claims 2 to 10, in which said medicament (a) has a median particle size not exceeding $10\mu\text{m}$.

15 12. A combination product as claimed in claim 11, in which said medicament (a) has a median particle size not exceeding $5\mu\text{m}$.

13. A combination product as claimed in claim 12, in which said medicament (a) has a median particle size of less than $3\mu\text{m}$.

20 14. A combination product as claimed in any one of claims 1 to 13, in which the antiasthma drug comprises one or more respiratory drugs selected from the group consisting of β_2 -agonists, steroids, cromones, antimuscarinic drugs and leukotriene receptor antagonists.

25 15. A combination product as claimed in any one of claims 1 to 14, which comprises one or more said antiasthma drugs in an amount of up to 10 parts by weight per hundred parts by weight of said first and second components of medicament (a) in combination.

30 16. A delivery device as claimed in claim 15, which comprises one or more said respiratory drugs in an amount of up to one part by weight per hundred parts by weight of said

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first and second components of medicament (a) in combination.

17. A combination product as claimed in any one of claims 1 to 16, in which ingredient (b) comprises a β_2 -agonist.

18. A combination product as claimed in any one of claims 1 to 16, in which ingredient (b) comprises a steroid.

19. A combination product as claimed in any one of claims 1 to 16, in which ingredient (b) comprises a cromone.

20. A combination product as claimed in any one of claims 1 to 16, in which ingredient (b) comprises a leukotriene receptor antagonist.

21. A combination product as claimed in any one of claims 1 to 16, in which ingredient (b) comprises an antimuscarinic drug.

22. A combination product as claimed in any one of claims 1 to 21, in which at least ingredient (a) is arranged to be delivered to a patient in the form of at least one individual inhalable dose, the or each individual dose comprising said ingredient (a) in an amount of at least 10mg.

23. A combination product as claimed in claim 22, in which the or each individual dose comprises said first and second components in a combined amount of at least 25mg.

24. A combination product as claimed in claim 23, in which the or each dose comprises said ingredient (a) in a combined amount of at least 40mg.

25. A combination product as claimed in any one of claims 22 to 24, in which at least ingredient (a) is arranged for sequential delivery of a multiplicity of inhalable doses.

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26. A combination product as claimed in any one of claims 1 to 25, in which the antiasthma drug is arranged for delivery in admixture with ingredient (a).

27. A combination product as claimed in any one of
5 claims 1 to 26, in which the antiasthma drug is arranged for delivery separately from, and simultaneously or sequentially with, ingredient (a).

28. A pack for use as part of a combination product according to any one of claims 1 to 27, said pack including
10 a delivery device for delivery of ingredient (a) to a patient and further comprising instructions to use said delivery device in a method of treatment including the separate simultaneous or sequential administration of an antiasthma drug.

29. A method of prevention and/or treatment of asthma, comprising administering to a patient at least one dose of a combination product as defined in any one of claims 1 to 27.

30. A delivery device for administering to a patient by inhalation a medicament for the prevention and/or
20 treatment of asthma, the delivery device containing a medicament comprising a surface active phospholipid (SAPL) composition in finely divided form, the SAPL including a component which enhances the spreading of the medicament, the delivery device being arranged for delivery of at least
25 one individual dose in an amount of at least 10mg.

31. A delivery device for administering to a patient by inhalation a medicament for the prevention or treatment of asthma, the delivery device containing a medicament comprising a first component consisting of one or more
30 phosphatidyl cholines and a second component consisting of one or more compounds selected from the group consisting of phosphatidyl glycerols, phosphatidyl ethanolamines, phosphatidyl serines, phosphatidyl inositols and chlorestyl

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palmitate, the delivery device being arranged for delivery of at least one individual inhalable dose, the or each individual dose comprising said first component and said second component in a combined amount of at least 10mg.

5 32. A delivery device as claimed in claim 30 or claim 31, in which the medicament is as defined in any one of claims 2 to 13.

 33. A delivery device as claimed in any one of claims 30 to 32, which further includes means for dispensing an
10 inhalable dose of an antiasthma drug.

 34. Use of (a) a surface active phospholipid (SAPL) composition in finely divided form conjointly with (b) an antiasthma drug in the manufacture of a medicament for the control of asthma.

15 35. A combination product for use in the prevention or treatment of asthma comprising

 (a) a medicament comprising a first phospholipid component which is capable of binding to lung tissue and a second component which is capable of enhancing the spreading
20 of said first component over an aqueous medium at 37°C, said medicament being in the form of a finely divided powder; and

 (b) an antiasthma drug;
the ingredients (a) and (b) being arranged for administration in combination or separately, simultaneously
25 or sequentially.

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ABSTRACT

In the Section of the Application that forms the Abstract, the final text is as follows:

ABSTRACT

Disclosed is a combination product for use in treating asthma and other respiratory conditions comprising a medicament comprising a surface active phospholipid composition in the form of a fine powder and an antiasthma drug. The product is arranged to be administered to the lungs by inhalation, for example, by the disclosed devices.

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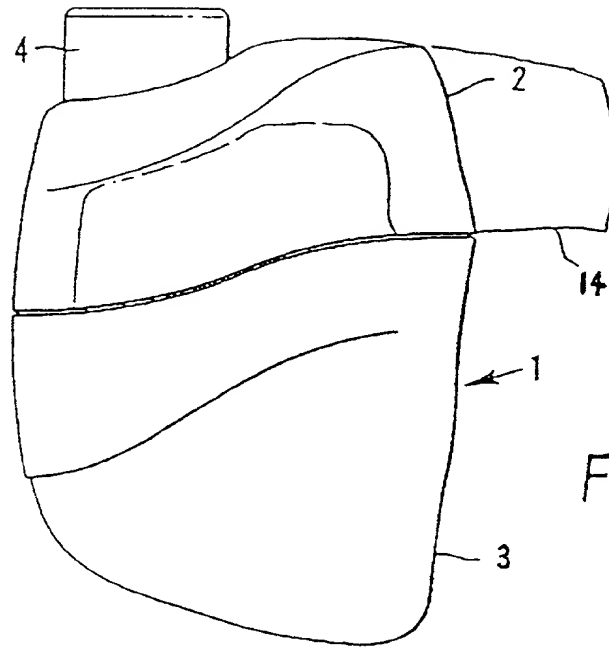


Fig. 1

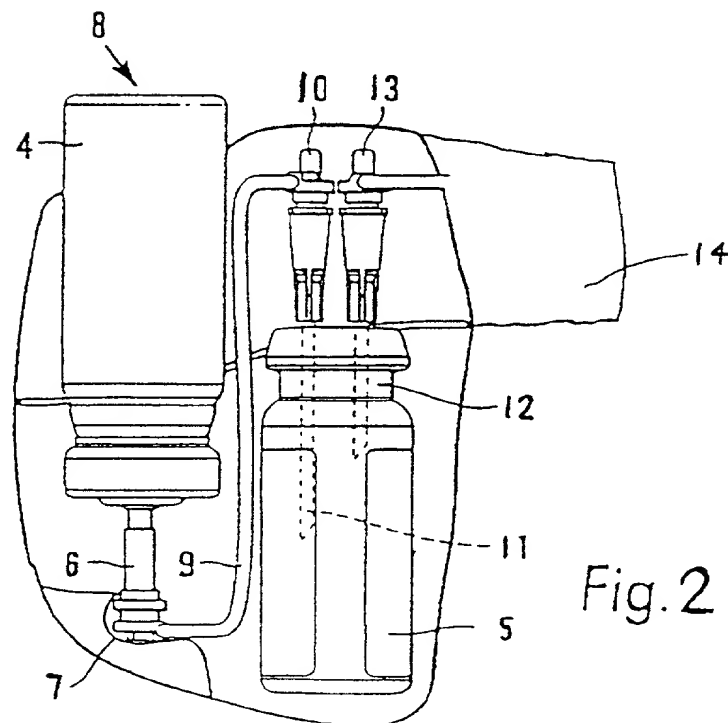


Fig. 2

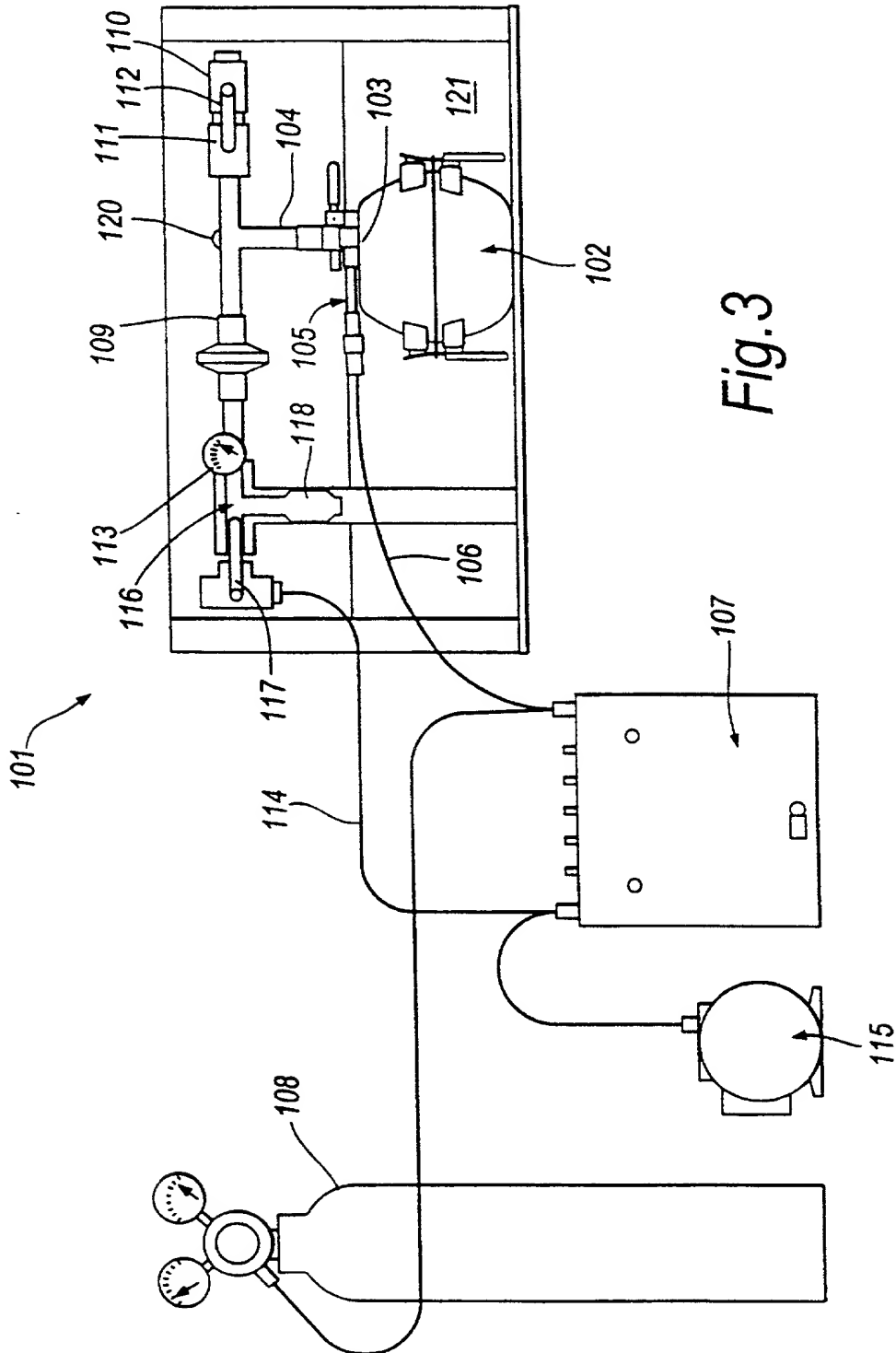


Fig.3



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DECLARATION

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or the below named inventors are the original, first and joint inventors (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled **Anti-Asthmatic Combinations Comprising Surface Active Phospholipids**, the Specification of which:

- ☐ is attached hereto.
☒ was filed on **May 22, 2001** as Application Serial No. **09/856,400**.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims.

I acknowledge the duty to disclose to the Patent and Trademark Office all information known to me to be material to patentability of the subject matter claimed in this application, as "materiality" is defined in Title 37, Code of Federal Regulations, § 1.56.

I hereby claim priority benefits under Title 35, United States Code, § 119 and/or § 365 of any foreign application(s) for patent or inventor's certificate, PCT international application(s), and United States provisional application(s), listed below and have also identified below any foreign application for patent or inventor's certificate, PCT international application, or United States provisional application, having a filing date before that of the application on which priority is claimed:

PRIORITY APPLICATION(S)			Priority Claimed
PCT/GB99/03952	PCT	November 26, 1999	Yes
(Number)	(Country)	(Date Filed)	Yes/No
9912639.3	GB	May 28, 1999	Yes
(Number)	(Country)	(Date Filed)	Yes/No
PCT/GB98/03543	PCT	November 26, 1998	Yes
(Number)	(Country)	(Date Filed)	Yes/No

I hereby claim the benefit under Title 35, United States Code, § 120 and/or § 365 of any United States application(s) and PCT international application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT international application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose all information known to me to be material to patentability of the subject matter claimed in this application, as "materiality" is defined in Title 37, Code of Federal Regulations, § 1.56, which becomes available between the filing date of the prior application and the national or PCT international filing date of this application:

N/A

(Application Serial No.)	(Filing Date)	(Status)
--------------------------	---------------	----------

I hereby direct that all correspondence and telephone calls be addressed to Shelley P.M. Fussey, Williams, Morgan & Amerson, P.C., 7676 Hillmont, Suite 250, Houston, Texas 77040, (713) 934-7000.

I hereby declare that all statements made of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of The United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

16

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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Hills *et al.*

Serial No.: 09/856,400

Filed: May 22, 2001

For: Anti-Asthmatic Combinations
Comprising Surface Active
Phospholipids

§
§
§ Group Art Unit: Unknown
§
§ Examiner: Unknown
§
§ Atty. Dkt.: 4040.000300
§
§
§
§

ELECTION UNDER 37 C.F.R. §§ 3.71 AND 3.73
AND POWER OF ATTORNEY

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

The undersigned, being Assignee of record of the entire interest in the above-identified application by virtue of an assignment recorded in the United States Patent and Trademark Office as set forth below, hereby elects, under 37 C.F.R. § 3.71, to prosecute the application to the exclusion of the inventor.

The Assignee hereby revokes any previous Powers of Attorney and appoints:

Danny L. Williams, Reg. No. 31,892; Terry D. Morgan, Reg. No. 31,181; J. Mike Amerson, Reg. No. 35,426; Kenneth D. Goodman, Reg. No. 30,460; Jeffrey A. Pyle, Reg. No. 34,904; Randall C. Furlong, Reg. No. 35,444; Scott F. Diring, Reg. No. 35,119; George J. Oehling, Reg. No. 40,471; Shelley P.M. Fussey, Reg. No. 39,458; Mark D. Moore, Reg. No. 42,903; Louis H. Iselin, Reg. No. 42,684; Raymund F. Eich, Reg. No. 42,508; Bradley A. Misley, Reg. No. 46,937; Thomas H. Belvin, Jr., Reg. No. 43,491; Daren C. Davis, Reg. No. 38,425; and Stephanie A. Wardwell, Reg. No. 48,025;

each an attorney or agent with the law firm of WILLIAMS, MORGAN & AMERSON, P.C., as its attorney or agent so long as they remain with such law firm, with full power of substitution and revocation, to prosecute the application, to make alterations and amendments therein, to transact all business in the Patent and Trademark Office in connection therewith, and to receive any Letters Patent, and for one year after issuance of such Letters Patent to file any request for a certificate of correction that may be deemed appropriate.

Pursuant to 37 C.F.R. § 3.73, the undersigned has reviewed the evidentiary documents, specifically the Assignment to Britannia Pharmaceuticals Limited referenced below, and certifies that to the best of my knowledge and behalf, title remains in the name of the Assignee.

09856400-001701

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BY: J. A. Shepard
Name: J. A. SHEPARD
Title: COMPANY SECRETARY

Date: 13 August 2001

ASSIGNMENT:

☒
☐

Concurrently filed
Previously recorded

Date: _____
Reel: _____
Frame: _____

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